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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MINNIFIELD, NITA M	

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1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,916	KRIEG ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-35,37-48,50-66,68-79 and 81-112* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 24,31,34,38,45,47,55,62,65,69,76,78,85,88,93,95,101,104,109 and 111.

Continuation of Disposition of Claims: Claims rejected are 19-23,25-30,32,33,35,37,39-44,46,48,50-54,56-61,63,64,66,68,70-75,77,79,81-84,86,87,89-92,94,96-100,102,103,105-108,110 and 112.

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed December 5, 2007 is acknowledged and has been entered. Claims 1-18, 36, 49, 67 and 80 have been canceled. Claims 19-35, 37-48, 50-66, 68-79 and 81-112 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 19-23, 25-30, 32, 33, 35, 37, 39-44, 46, 48, 50-54, 56-61, 63, 64, 66, 68, 70-75, 77, 79, 81-84, 86, 87, 89-92, 94, 96-100, 102, 103, 105-108, 110 and 112 read on the elected invention/elected species and will be examined in the instant application.

4. This application contains claims 23, 31, 34, 38, 45, 47, 55, 62, 65, 69, 76, 78, 85, 88, 93, 95, 101, 104, 109 and 111 drawn to an invention nonelected with traverse in the reply filed on May 26, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 19-22, 32, 33, 35, 37, 46, 48, 50-52, 63, 64, 66, 68, 77, 79, 81, 82, 83(c), 86, 87, 89, 90, 91(c), 94, 96-98, 99(c), 102, 103, 105, 106, 107(c), 110 and 112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The pending claims (for example claim 19) are a method for treating a mycobacterial infection in a subject, the method comprising administering to a subject an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide, in an amount effective to treat or ameliorate an infection with a Mycobacterium bacterium, thereby treating the infection in the subject. Other claims are directed to methods for treating, preventing or ameliorating an infection in a subject, or stimulating in a subject an immune response against a Mycobacterium bacterium, or amounts of CpG effective to inhibit replication of a Mycobacterium bacterium, or administering results in induction of an immune response effective to protect the subject against onset of disease or to decrease severity of symptoms of disease caused by infection by the Mycobacterium bacterium, or administer to a subject multiple doses of the CpG (see independent claims 19, 37, 50, 68, 81, 90, 97 and 106). The composition administered is a CpG dinucleotide.

A review of the specification discloses a list of immunostimulatory nucleic acids that could be used in the claimed invention. The claims, claim 19 for

example, only provide that the immunostimulatory nucleic acid has 2 nucleotides (C and G). However, the specification does not teach an immunostimulatory nucleic acid molecule having only 2 nucleic acids, an unmethylated CpG dinucleotide as set forth in the claims. The claims do not set forth a structure for the claimed immunostimulatory nucleic acid molecule.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry,, whatever is now claimed. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing

distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of an immunostimulatory nucleic acid molecule, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of compositions, the skilled artisan could not immediately recognize or distinguish members of the claimed antigenic compositions. In view of the above, the instant specification fails to meet the written description requirement as set forth under 35 U.S.C. 112, first paragraph.

A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559,1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original); Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000) ("the specification does not clearly disclose to the skilled artisan that the inventors ... considered the ratio... to be part of their invention .... There is therefore no force to Purdue's argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which the [later-filed] claims carved out a patentable portion").

A specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose. Cooper v. Goldfarb, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998). See also UMC Elecs. Co. v. United States, 816 F.2d 647,

652, 2 USPQ2d 1465, 1468 (Fed. Cir. 1987) ("[T]here cannot be a reduction to practice of the invention without a physical embodiment which includes all limitations of the claim."); Estee Lauder Inc. v. L'Oreal, S.A., 129 F.3d 588, 593, 44 USPQ2d 1610, 1614 (Fed. Cir. 1997) ("[A] reduction to practice does not occur until the inventor has determined that the invention will work for its intended purpose."); Mahurkar v. C.R. Bard, Inc., 79 F.3d 1572, 1578, 38 USPQ2d 1288, 1291 (Fed. Cir. 1996) (determining that the invention will work for its intended purpose may require testing depending on the character of the invention and the problem it solves).

For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. >As explained by the Federal Circuit, "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met … even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also Capon v. Eshhar, 418 F.3d at 1358, 76 USPQ2d at 1084 ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were

novel combinations of known DNA segments.).< For example, disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. Noelle v. Lederman, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (holding there is a lack of written descriptive support for an antibody defined by its binding affinity to an antigen that itself was not adequately described). Additionally, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. See Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966 ("written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention"). A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." Eli Lilly, 119 F.3 at 1568, 43 USPQ2d at 1406. See also Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent

did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.").

It is noted that Applicants have claimed a large genus of CpG immunostimulatory nucleic acid molecules with only the C and G being defined in the immunostimulatory nucleic acid molecule. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir.

2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.) On the other hand, there may be situations where one species adequately supports a genus. See, e.g., Rasmussen, 650 F.2d at 1214, 211 USPQ at 326-27 (disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered); In re Herschler, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description."); In re Smythe, 480 F.2d 1376, 1383, 178 USPQ

279, 285 (CCPA 1973) (the phrase "air or other gas which is inert to the liquid" was sufficient to support a claim to "inert fluid media" because the description of the properties and functions of the air or other gas segmentizing medium would suggest to a person skilled in the art that appellant's invention includes the use of "inert fluid" broadly.).

It is noted that the 112, first paragraph written description rejection is maintained only for claims (19-22, 32, 33, 35, 37, 46, 48, 50-52, 63, 64, 66, 68, 77, 79, 81, 82, 83(c), 86, 87, 89, 90, 91(c), 94, 96-98, 99(c), 102, 103, 105, 106, 107(c), 110 and 112) that recite that the immunostimulatory nucleic acid molecule comprises an ummethylated CpG dinucleotide. Applicants' arguments set forth in the amendment filed December 5, 2007 have been fully considered but they are not persuasive. Applicants have asserted that the claims are readable upon methods using immunostimulatory nucleic acid sequences that are characterized by the presence of a CpG motif, rather than limited to CpG dinucleotides. Applicants have asserted that the specification discloses over 300 ODNs of various lengths and sequences with and without a CpG, either methylated or unmethylated, were synthesized and tested for their immunostimulatory activity and the unmethylated CpG motif conferred the observed immunostimulatory effect. Applicants have asserted that they have sufficiently described the scope of the claimed genus. However, it is the Examiner's position that the scope of the claims are readable on a CpG dinucleotide, which the over 300 ODNs of various lengths do not describe for treatment and prevention in the claimed method. The claims read on immunostimulatory nucleic acid molecules that are less than the 6 nucleotides (the lower limit of immunostimulatory nucleic acid molecules shown in the

specification) for the treatment and prevention of mycobacterial infection in a subject as presently claimed.

7. Claims 19-23, 25-30, 32, 33, 35, 37, 39-44, 46, 48, 50-54, 56-61, 63, 64, 66, 68, 70-75, 77, 79, 81-84, 86, 87, 89-92, 94, 96-100, 102, 103, 105-108, 110 and 112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods for treating a mycobacterium infection, generically (and specifically, tuberculosis) in a subject, the method comprising: administering to a subject an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide (i.e. see various formulas in claims 26-29 for example, GTCGTT), in an amount effective to treat, prevent or ameliorate an infection with a Mycobacterium bacterium (for example *M. tuberculosis*), thereby treating the infection (mycobacterium) in the subject.

A review of the specification discloses a list of immunostimulatory nucleic acids that could be used in the claimed invention. However, they comprise 8 or more nucleotides (see for example Tables 1, 2, 5, 9, 10), not the 2 nucleotides as set forth in claim 19. It is noted that Applicants' specification indicates that ODNs shorter than 8 bases were non-stimulatory (p. 19, l. 4-5).

The state of the art is unpredictable with regard to the use of oligonucleotides of less than 8 nucleotides having immunostimulatory activity. Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122)

teaches that "immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less in length were not as active even if they possessed the palindromic sequences. These results indicate that the immunostimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases long." (abstract).

The specification does not teach any of the methods as set forth in the instant claims for treating, preventing or ameliorating mycobacterium infections in a subject. The specification teaches numerous in vitro experiments, however these data do not indicate enablement for the claimed invention. The specification does not teach that any of the myriad of possibilities of CpG immunostimulatory nucleic acid molecule having the claimed formulas can be used to treat, prevent or ameliorate mycobacterium infection and specifically infection caused by *M. tuberculosis* in a subject.

It is noted that none of the claims recite the administration of an antigen from a mycobacterium bacterium. Neither the specification nor the state of the art teach or enable an immunostimulatory nucleic acid molecule alone treating, preventing or ameliorating a mycobacterium infection in a subject.

The state of the art with regard to CpG and treating, preventing or ameliorating mycobacterium infection and specifically infection caused by *M. tuberculosis* in a subject is unpredictable. The history of vaccination in humans (the scope of the instant claims) against Mycobacterium disease (tuberculosis) is notorious for lack of a successful protection (i.e. prevention) as well as amelioration. At the time of filing, there still remained a lack of correlation of

success in animal models with successful vaccination of humans against mycobacterial disease, as evidenced by (Wiegeshaus, E.H. et al, Reviews of Infectious Diseases, April 1989, 11/Suppl. 2:S484-S490). Animal models used to evaluate the relative protective potency of a panel of tuberculosis vaccines have yielded dissimilar data (abstract). Wiegeshaus et al teaches that animal models have produced disparate data on the protective potency of tuberculosis vaccines, therefore the variables comprising such models cannot be randomly chosen and that it is not known which animal model, if any, predicts the protective potency of vaccines for humans (page S490). Griffin et al (Trends in Microbiology, Nov. 1995, 3/11: 418-424) teaches that limitations in the design of field studies have seriously compromised our ability to evaluate the efficacy of bacilli Calmette-Guerin (BCG) in human and animal populations accurately. Griffin et al teaches that humans, cattle, deer, guinea pigs and rabbits have similar pathology but differ in their susceptibility to tuberculosis (p. 418). Griffin et al teaches that although studies in guinea pigs and rabbits have made an important contribution to our understanding of virulence and pathogenesis of tuberculosis they have limited use for the study of the protective immune response (page 418-419). Griffin et al teaches that multiple factors influence the development of protective immunity to mycobacterium are complex and difficult to characterize and considering the variables the influence experimental infection and protective immunity it is essential to develop standardized animal models and test systems to define the immune parameters in vivo and in vitro that protect against virulent myco-bacterium. Griffin et al teach that the lack of agreement about the efficacy of BCG seen after 60 years of its widespread use in more that 3 billion humans and the variable results from extensive laboratory animal studies suggest that further

empirical studies are unlikely to help in assessing the efficacy of new generation vaccines against tuberculosis. Griffith et al teaches that it is essential to exploit the theoretical knowledge obtained from laboratory studies and to develop definitive in vitro markers of protective immunity in parallel with infection studies that evaluate functional protection in vivo (page 419). Griffin et al further teach that many critical factors that are required to generate protective immunity and target the cellular pathways for appropriate T cell activation and effector activity against tuberculosis have been identified and the ability to exploit this knowledge depends on relevant animal models being available to test new candidate vaccines (pages 422-423).

The prior art has shown that limitations in the design of field studies have seriously compromised our ability to evaluate the efficacy of Mycobacterium vaccines in human and animal populations accurately, they differ in their susceptibility to tuberculosis and animals models have limited use for the study of the protective immune response. The prior art has also shown that multiple factors that influence the development of protective immunity to mycobacterium are complex and difficult to characterize. The prior art has taught that there are many variables that influence experimental infection and protective immunity and that it is essential to develop standardized animal models and test systems to define the immune parameters in vivo and in vitro that protect against virulent mycobacterium. The prior art has also shown the limitations of using guinea pigs or mouse models to evaluate protective immunity.

Applicants' arguments set forth in the amendment filed ***February 15, 2007*** have been fully considered but they are not persuasive. Applicants have asserted

that Wiegeshaus or Griffin et al discuss the state of the art of animal models in the treatment of tuberculosis in humans. Applicants have asserted that neither Wiegeshaus nor Griffin et al describe the use of CpG oligonucleotides as adjuvants in this system. A general teaching regarding animal models for vaccines generally is not sufficient to establish the unpredictability of CpG nucleic acids as vaccine adjuvants. However, it is noted that these references were cited to show that the state of the art with regard to treatments and vaccines for mycobacterium infections and in particular tuberculosis was and is unpredictable. Further, Tomioka (Current Pharmacological Design, 2004, 10:3297-3312) teaches that since "ISS-ODN is efficacious in potentiating the therapeutic use of CAM in MAC-infected mice, this agent appears to be useful for adjunctive immunotherapy of mycobacterial infections, when used in combination with conventional chemotherapy." (p. 3309, left col.) "At present, clinical management of patients with these mycobacterial infections faces difficult problems, such as the worldwide emergence and increase in prevalence of MDR-MTB strains, the worldwide increase in AIDS-associated disseminated MAC infections, and the gradual but steady progression of pulmonary MAC infections in patients of advanced age even receiving anti-MAC multidrug regimens in industrialized countries. In order to cope with these difficulties, development of new drugs with much greater antimycobacterial activity than those of ordinary antituberculous or anti-MAC drugs is urgently desired." (p. 3309, right column; see also p. 3310) Further, Hsieh et al (Vaccine, 2004, 22:655-659) teaches that "[T]o determine if this would improve subunit vaccination of mice CpG ODN were added to a subunit vaccine consisting of the culture filtrate proteins (CFP) of Mycobacterium tuberculosis H37Rv. It was observed that although adding CpG ODN to the vaccines promoted substantially increased IFNγ, production by lymph node cells draining sites of inoculation, this failed to translate after aerosol challenge into any degree of enhancement of bacterial clearance in the lungs, influx of IFN-positive T cells, or changes in histopathology. These data suggest that the vaccine enhancing effects of CpG ODN are relatively transient." (Abstract) The art does not teach the use of CpG alone as mycobacterium tuberculosis vaccines, nor in the treatment or amelioration of mycobacterium bacterium infections in a subject.

The state of the art is unpredictable with regard to treatments using CpG. CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms (See Krieg et al, Weiner and McCluskie et al for recent advances using CpG oligonucleotides). Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (See McCluskie et al in

its entirety, and especially on page 296; see Krieg et al on page 524). Weiner states furthermore that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (See especially page 461). Further, Weiner cautions that despite therapeutic promise of some CpG ODNs, all CpG ODNs are not alike and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset or CpG ODN sequence. Weiner teaches that the clinical effects of CpG ODN have not yet been explored and further work with the immunostimulatory nucleic acids in both the laboratory and the clinic are needed before their true promise as investigational immunological and therapeutic agents is known.

Applicants' arguments set forth in the amendment filed ***February 15, 2007*** have been fully considered but they are not persuasive. With regard to Applicants' arguments concerning McCluskie et al, it is noted that the claimed encompass DNA vaccines. The claims recite "an immunostimulatory nucleic acid molecule comprising…". Applicants have asserted that Krieg et al at p. 524 states that it should be stressed that CpG ODN is effective in asthma immunotherapy even when given as a stand-alone agent without allergen. However, this does not address the enablement of the claimed invention. Because CpG ODN may be effective in asthma immunotherapy does not indicate the CpG ODN will be effective as a stand-alone agent in the treatment, prevention, amelioration of mycobacterium bacterium infection in a subject. With regard to O'Hagan et al, it is noted that O'Hagan et al teaches that an antigen is needed to have good results. The instant specification does not teach that administration of an antigen conjugated to CpG ODN or CpG ODN alone will treat, prevent or ameliorate mycobacterium infection in a subject as now claimed.

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention. The skilled artisan would not reasonably expect success in using animal models to assess protective immunity against Mycobacterium infections in humans because they differ in their susceptibility to Mycobacterium infections, in particular tuberculosis nor would the skilled artisan expect success using an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide to treat, prevent or ameliorate mycobacterium infection (tuberculosis) in a subject. The skilled artisan cannot conclude from the absence of data in the specification and the state of the prior art that an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide can treat, prevent or ameliorate mycobacterium infection (tuberculosis) in a subject because the prior art regarding the use of animal models in assessing protective immunity for

Mycobacterium infections (tuberculosis) is unpredictable and not well established. The specification is devoid of data to support that the claimed method can successfully to treat, prevent or ameliorate mycobacterium infection (tuberculosis) in a subject using an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide. There are no animal models. This demonstration is necessary to enable the claimed methods. It is noted that the claims only indicate that the CpG is administered. The state of the art with regard to such a method is unpredictable, as well. O'Hagan et al 2001 does teach that the CpG has adjuvant properties and that this effect appears to be maximized by their conjugation to protein antigens or their formulation with delivery systems (p. 75). There is no evidence of record or in the state of the art that indicates that CpG administered alone will be successful in the treatment, prevention or amelioration of Mycobacterium infections (tuberculosis) in a subject, human or otherwise. O'Hagan et al teaches that "[A]lthough, it is too early to know in which situations CpG oligo's might prove to be most advantageous, their apparent ability to selectively manipulate Th1 responses is most exciting. Nevertheless, the safety of CpG DNA needs to be firmly established in the clinic, since the induction of autoimmunity with CpG immunization can be shown in various established animals models (citation omitted). However, the relevance of these observations to human studies is unknown." (p. 75)

There are no working examples in the instant specification that show the claimed methods can treat, prevent or ameliorate Mycobacterium infection (tuberculosis) in a subject. The skilled artisan cannot conclude that a protective immune response can be achieved using any host with the information provided in the specification and an undue amount of experimentation would be necessary to practice the claimed invention by using the limited information disclosed in the specification. Therefore, the specification fails to enable the claimed invention.

The state of the art post-filing as well as the specification indicates that the scope and breath of the claimed invention is not enabled. The claims contemplate a myriad of possible oligonucleotides having the CpG motif and range in size from 8 to 100 nucleotides (see claims 26-29 for example) and unlimited nucleotides (see claim 19 for example). The specification has not shown that the myriad oligonucleotides contemplated by the claims will function in a method that treats, prevents or ameliorates mycobacterium infections (tuberculosis) in a subject.

It is noted that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that any of the claimed methods would function *in vivo* or *in vitro*. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used

herein refers to the relationship between *in vitro* or *in vivo* animal model assays and disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples. (see MPEP 2164.02) The pending specification does not set forth such correlations for a working example of the claimed *in vivo* method.

Applicants' arguments set forth in the amendment filed ***February 15, 2007*** have been fully considered but they are not persuasive. Applicants have asserted that the "in vitro data presented in the specification is sufficient to support the claimed invention. Applicants have described a class of molecules (nucleic acids) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Thl response being favored. This class of oligonucleotides is described throughout the specification and their ability to produce an immune response is not only described (e.g., see page 8, lines 22-23 and 25-27, page 9, lines 8-9 and page 53, line 26 - page 54, line 5) but data is presented in vitro and in vivo using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The data in the application, including that represented in Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation. More than 40 oligonucleotides were tested. The data represented in Table 5 demonstrates that the immune stimulation has the characteristic pattern of a Thl response. Eleven different oligonucleotides induced a Thl cytokine profile, demonstrating the consistent stimulatory effect of CpG containing oligonucleotides." (Remarks, p. 18) However, the experiments and data set forth above do not directly address the enablement of the claimed method, specifically a method of treating a mycobacterial infection in a subject comprising administering to the subject an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide, in an amount effective to treat, prevent or ameliorate a mycobacterium bacterium infection in a subject, thereby treating the infection in the subject. This information does not set forth enablement that the immunostimulatory nucleic acid molecule can protect against mycobacterium bacterium infection in a subject as presently claimed. None of the in vitro or in vivo data set forth in the instant specification enables the claimed invention.

The claimed invention must be enabled as of the filing date of the patent application, not enabled by publications post filing. Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial

inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b).

The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. 35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used. (see MPEP 2164.05(a))

The specification need not disclose what is well known to those skilled in the art and preferably omits that which is well known to those skilled and already available to the public. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application").< Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of

the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled.

Further, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). Although, typically, inoperative embodiments are excluded by language in a claim (e.g., preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. In re Angstadt, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). However, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is

involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the claimed invention without undue experimentation. In *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated: Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification using the claimed methods to treat Mycobacterium infections (tuberculosis) in subject administering a CpG immunostimulatory nucleic acid molecule as previously stated, 3) there are no working examples presented in the specification that teach the claimed methods to treat, prevent or ameliorate Mycobacterium infections as previously stated, 4) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level), and 5) the state of the art in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In view of all of the above, the pending specification does not enable the claimed invention and therefore the pending claims are not enabled. For reasons stated above (i.e. lack of enabling disclosure, unpredictability of the art, lack of guidance) it would require undue experimentation to practice the claimed invention.

The rejection is maintained for the reasons of record. Applicants' arguments set forth in the amendment filed December 5, 2007 have been fully considered but they are not persuasive. The Examiner acknowledges the error on page 12 of the last Office Action. Claim 19 recites a CpG dinucleotide. Applicants have asserted that "A mycobacterium infection is caused by a pathogen, mycobacterium, entering and infecting a host and resulting in pathogenic conditions such as tuberculosis. It has been known in the art that a host immune system responds to such pathogens by activating a number of immune responses, including the innate immunity and the adaptive immunity. The former is generally an early (or already existing) response and involves primarily the action of Natural Killer (NK) cells, which can provide a defense against pathogens. In addition, as part of the adaptive immunity, B cells perform the role of immune surveillance, thereby promoting antibody production. Indeed, the instant application provides, *inter alia,* a number of working examples demonstrating that CpG-containing immunostimulatory oligonucleotides can activate lymphocytes, such as NK cells and B cells. Thus, contrary to the Examiner's position, the instant application presents data to support that administration of an immunostimulatory CpG oligonucleotide can stimulate a subject's immune response in such a way that would facilitate the body's defense against an infection. The skilled artisan would therefore reasonably conclude that such an agent that can enhance or stimulate the immune response would have a beneficial effect for a subject infected with mycobacterium to promote an immunological defense against the pathogen." (Remarks, p. 23) However, it is the Examiner's position that these in vitro assays showing activation of lymphocytes such as NK cells and B cells is not an indication of a successful method for treating, ameliorating, or preventing a mycobacterium infection, generically (and

specifically, tuberculosis) in a subject, the method comprising: administering to a subject an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide (i.e. see various formulas in claims 26-29 for example, GTCGTT), in an amount effective to treat, prevent or ameliorate an infection with a Mycobacterium bacterium (for example *M. tuberculosis*), thereby treating the infection (mycobacterium) in the subject. The state of the art is unpredictable with regard to the use of oligonucleotides of less than 8 nucleotides having immunostimulatory activity. Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122) teaches that "immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less in length were not as active even if they possessed the palindromic sequences. These results indicate that the immunostimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases long." (abstract).

The Examiner acknowledges and appreciates the Fertel et al reference that Applicants provided, however this does not address the lack of enablement of the claimed invention.

8. No claims are allowed.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-8975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N. M. Minnifield/
Primary Examiner,
Art Unit 1645
March 2, 2008